Figure 1

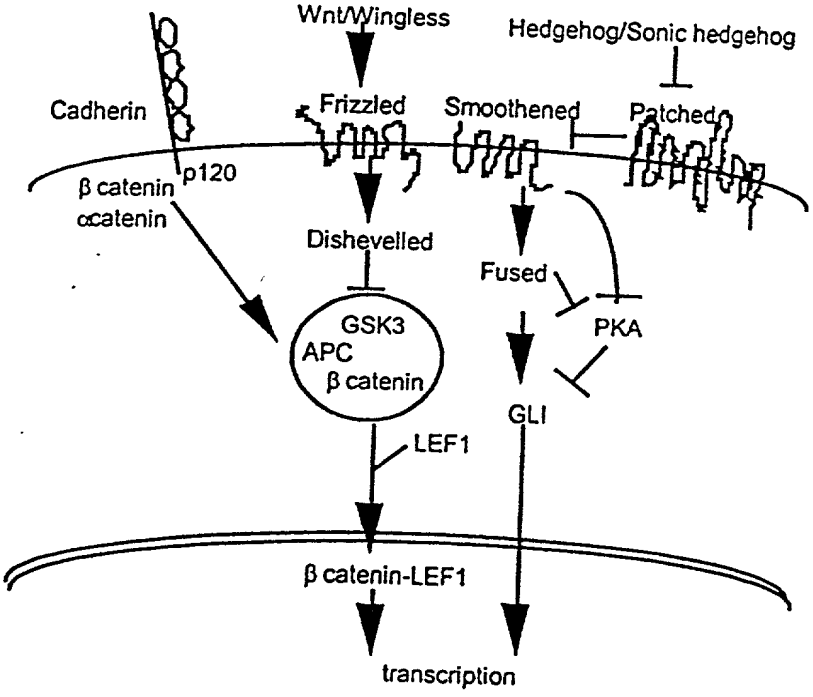

Wnt/Wingless
Hedgehog/Sonic hedgehog
Cadherin
Frizzled
Smoothened
Patched
p120
β catenin
αcatenin
Dishevelled
Fused
GSK3
APC
β catenin
PKA
GLI
LEF1
β catenin-LEF1
transcription

Figure 2a

Alignment of several frizzled family members

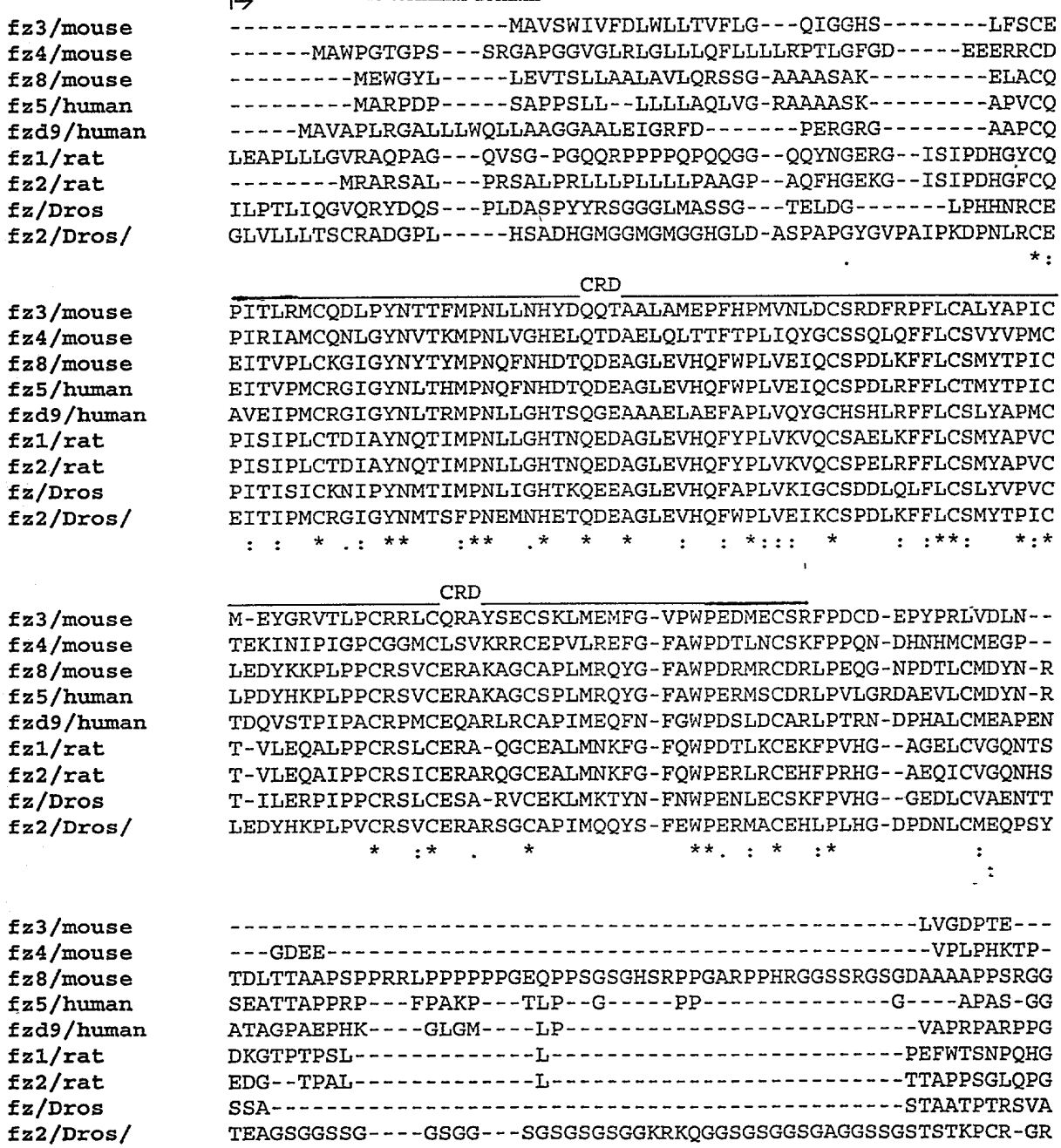


Figure 2b

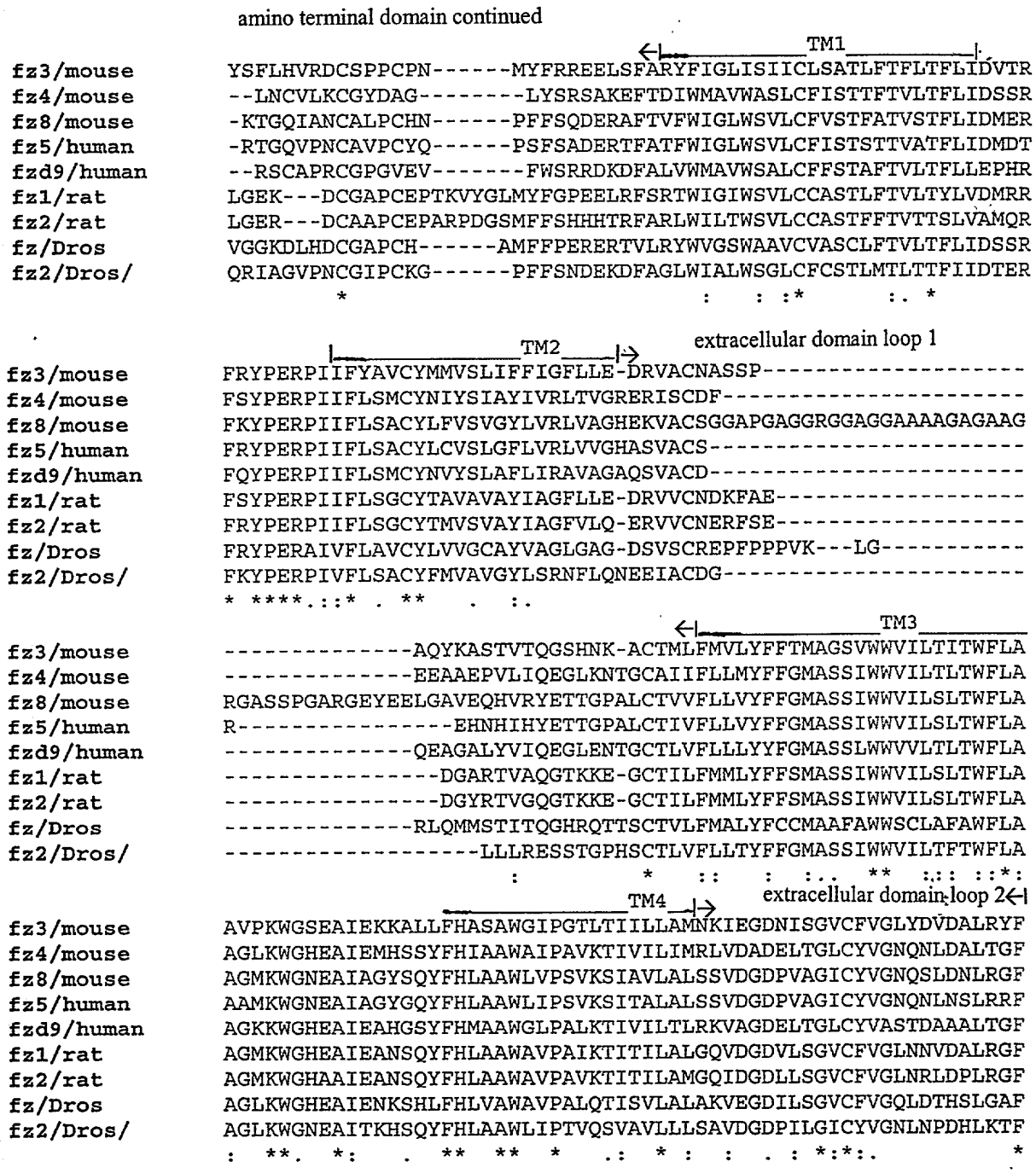

amino terminal domain continued
TM1
fz3/mouse YSFLHVRDCSPPCPN------MYFRREELSFARYFIGLISIICLSATLFTFLTFLIDVTR
fz4/mouse --LNCVLKCGYDAG--------LYSRSAKEFTDIWMAVWASLCFISTTFTVLTFLIDSSR
fz8/mouse -KTGQIANCALPCHN------PFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLIDMER
fz5/human -RTGQVPNCAVPCYQ------PSFSADERTFATFWIGLWSVLCFISTSTTVATFLIDMDT
fzd9/human --RSCAPRCGPGVEV-------FWSRRDKDFALVWMAVWSALCFFSTAFTVLTFLLEPHR
fz1/rat LGEK---DCGAPCEPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRR
fz2/rat LGER---DCAAPCEPARPDGSMFFSHHHTRFARLWILTWSVLCCASTFFTVTTSLVAMQR
fz/Dros VGGKDLHDCGAPCH------AMFFPERERTVLRYWVGSWAAVCVASCLFTVLTFLIDSSR
fz2/Dros/ QRIAGVPNCGIPCKG------PFFSNDEKDFAGLWIALWSGLCFCSTLMTLTTFIIDTER
TM2
extracellular domain loop 1
fz3/mouse FRYPERPIIFYAVCYMMVSLIFFIGFLLE-DRVACNASSP----------
fz4/mouse FSYPERPIIFLSMCYNIYSIAYIVRLTVGRERISCDF----------
fz8/mouse FKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGRGGAGGAAAAGAGAAG
fz5/human FRYPERPIIFLSACYLCVSLGFLVRLVVGHASVACS----------
fzd9/human FQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACD----------
fz1/rat FSYPERPIIFLSGCYTAVAVAYIAGFLLE-DRVVCNDKFAE----------
fz2/rat FRYPERPIIFLSGCYTMVSVAYIAGFVLQ-ERVVCNERFSE----------
fz/Dros FRYPERAIVFLAVCYLVVGCAYVAGLGAG-DSVSCREPFPPPVK---LG----------
fz2/Dros/ FKYPERPIVFLSACYFMVAVGYLSRNFLQNEEIACDG----------
TM3
fz3/mouse ----------AQYKASTVTQGSHNK-ACTMLFMVLYFFTMAGSVWWVILTITWFLA
fz4/mouse ----------EEAAEPVLIQEGLKNTGCAIIFLLMYFFGMASSIWWVILTLTWFLA
fz8/mouse RGASSPGARGEYEELGAVEQHVRYETTGPALCTVVFLLVYFFGMASSIWWVILSLTWFLA
fz5/human R----------EHNHIHYETTGPALCTIVFLLVYFFGMASSIWWVILSLTWFLA
fzd9/human ----------QEAGALYVIQEGLENTGCTLVFLLLYYFGMASSLWWVVLTLTWFLA
fz1/rat ----------DGARTVAQGTKKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz2/rat ----------DGYRTVGQGTKKE-GCTILFMMLYFFSMASSIWWVILSLTWFLA
fz/Dros ----------RLQMMSTITQGHRQTTSCTVLFMALYFCCMAAFAWWSCLAFAWFLA
fz2/Dros/ ----------LLLRESSTGPHSCTLVFLLTYFFGMASSIWWVILTFTWFLA
TM4
extracellular domain loop 2
fz3/mouse AVPKWGSEAIEKKALLFHASAWGIPGTLTIILLAMNKIEGDNISGVCFVGLYDVDALRYF
fz4/mouse AGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDADELTGLCYVGNQNLDALTGF
fz8/mouse AGMKWGNEAIAGYSQYFHLAAWLVPSVKSIAVLALSSVDGDPVAGICYVGNQSLDNLRGF
fz5/human AAMKWGNEAIAGYGQYFHLAAWLIPSVKSITALALSSVDGDPVAGICYVGNQNLNSLRRF
fzd9/human AGKKWGHEAIEAHGSYFHMAAWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGF
fz1/rat AGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVGLNNVDALRGF
fz2/rat AGMKWGHAAIEANSQYFHLAAWAVPAVKTITILAMGQIDGDLLSGVCFVGLNRLDPLRGF
fz/Dros AGLKWGHEAIENKSHLFHLVAWAVPALQTISVLALAKVEGDILSGVCFVGQLDTHSLGAF
fz2/Dros/ AGLKWGNEAITKHSQYFHLAAWLIPTVQSVAVLLLSAVDGDPILGICYVGNLNPDHLKTF

Figure 2c

```
                 ________________TM5____                                                    ______
fz3/mouse        VLAPLCLYVVVGVSLLLAGIISLNRVRIEIPLEKE-----NQDKLVKFMIRIGVFSILYL
fz4/mouse        VVAPLFTYLVIGTLFIAAGLVALFKIRSNLQK-DG----TKTDKLERLMVKIGVFSVLYT
fz8/mouse        VLAPLVIYLFIGTMFLLAGFVSLFRIRSVIKQQGGP---TKTHKLEKLMIRLGLFTVLYT
fz5/human        VLGPLVLYLLVGTLFLLAGFVSLFRIRSVIKQ-GG----TKTDKLEKLMIRIGIFTLLYT
fzd9/human       VLVPLSGYLVLGSSFLLTGFVALFHIRKIMKT-GG----TNTEKLEKLMVKIGVFSILYT
fz1/rat          VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEKLEKLMVRIGVFSVLYT
fz2/rat          VLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKH-DG----TKTEPLERLMVRIGVFSVLYT
fz/Dros          LILPLCIYLSIGALFLLAGFISLFRIRTVMKT-DG----KRTDKLERLMLRIGFFSGLFI
fz2/Dros/        VLAPLFVYLVIGTTFLMAGFVSLFRIRSVIKQQGGVGAGVKADKLEKLMIRIGIFSVLYT
                 :  *    : :*  :    .  :*  ::  :              . : ::  :: .*: *:
                 ______TM6_______|->    extracellular domain loop 3          <-|______
fz3/mouse        VPLLVVIGCYFYEQAYRGIWETTWIQERCREYHIPCPYQVTQMS-------RPDLILFLM
fz4/mouse        VPATCVIACYFYEISNWALFRYSADDS--------------------------NMAVEML
fz8/mouse        VPAAVVVACLFYEQHNRPRWEATHNCPCLRDLQPDQARR-------------PDYAVFML
fz5/human        VPASIVVACYLYEQHYRESWEAALTCACPGHDTGQPRAK-------------PEYWVLML
fzd9/human       VPATCVIVCYVYERLNMDFWRLRATEQPCAAAAGPGGRRDCSLP----GGSVPTVAVFML
fz1/rat          VPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQGGGGVPPHPPMSPDFTVFMI
fz2/rat          VPATIVIACYFYEQAFREHWERSWVSQHCKSLAIPCPAHYT-------PRTSPDFTVYMI
fz/Dros          LPAVGLLGCLFYEYYNFDEWMIQWHRDICKPFSIPCPAARAPGS----PEARPIFQIFMV
fz2/Dros/        VPATIVIGCYLYEAAYFEDWIKALACPCAQVK--GPGKK-------------PLYSVLML
                  *     :  .  . *                                          ::
                 __________TM7____
fz3/mouse        KYLMALIVGIPSIFWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNT
fz4/mouse        KIFMSLLVGITSGMWIWSAKTLHTWQKCS-----------NRLVNSGKVK-----REKRG
fz8/mouse        KYFMCLVVGITSGVWVWSGKTLESWRALC-----------TRCCWASKGAAVGAGAGGSG
fz5/human        KYFMCLVVGITSGVWIWSGKTVESWRRFT-----------SRCCCRPR-------RGHK-
fzd9/human       KIFMSLVVGITSGVWVWSSKTFQTWQSLC-----------YRKIAAGRARA----KACRA
fz1/rat          KYLMTLIVGITSGFWIWSGKTLNSWRKFY-----------TRLTNSK--------QGETT
fz2/rat          KYLMTLIVGITSGFWIWSGKTLHSWRKFY-----------TRLTNSR--------HGETT
fz/Dros          KYLCSMLVGVTSSVWLYSSKTMVSWRNFV-----------ERLQGKEPRT-----RAQAY
fz2/Dros/        KYFMALAVGITSGVWIWSGKTLESWRRFW-----------RRLLGAPDRTGANQALIKQR
                 :  :  :  *  :  .*: * **   :
```

Figure 3

Sequence alignment of a portion of the aminoterminal extracellular region of human Frizzled receptors

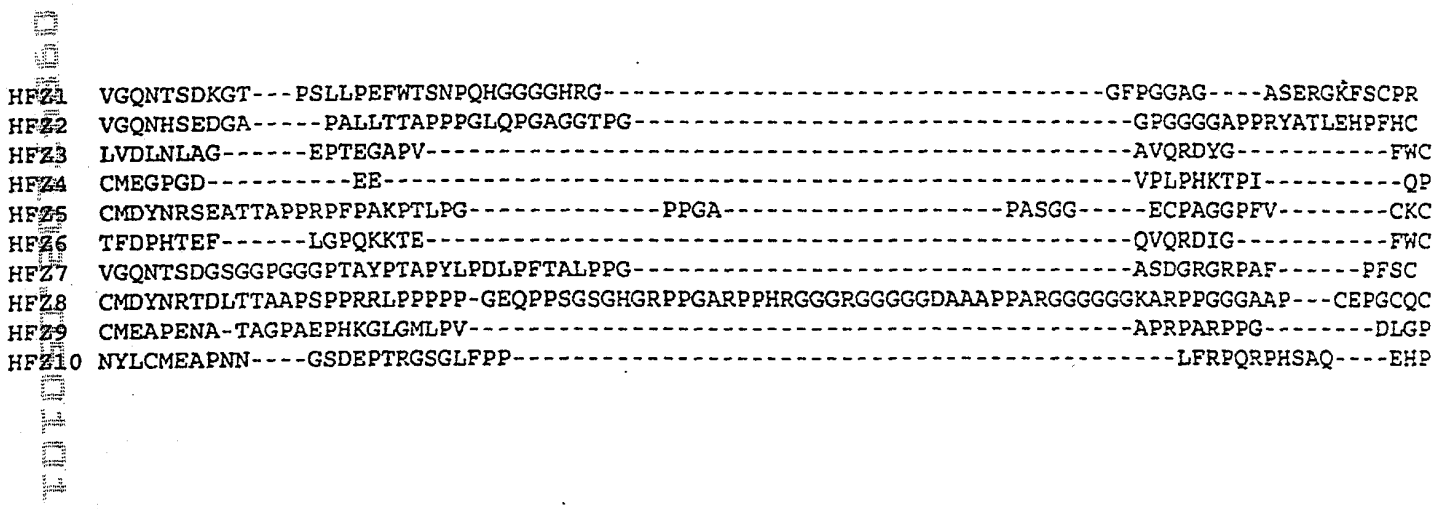


Figure 4

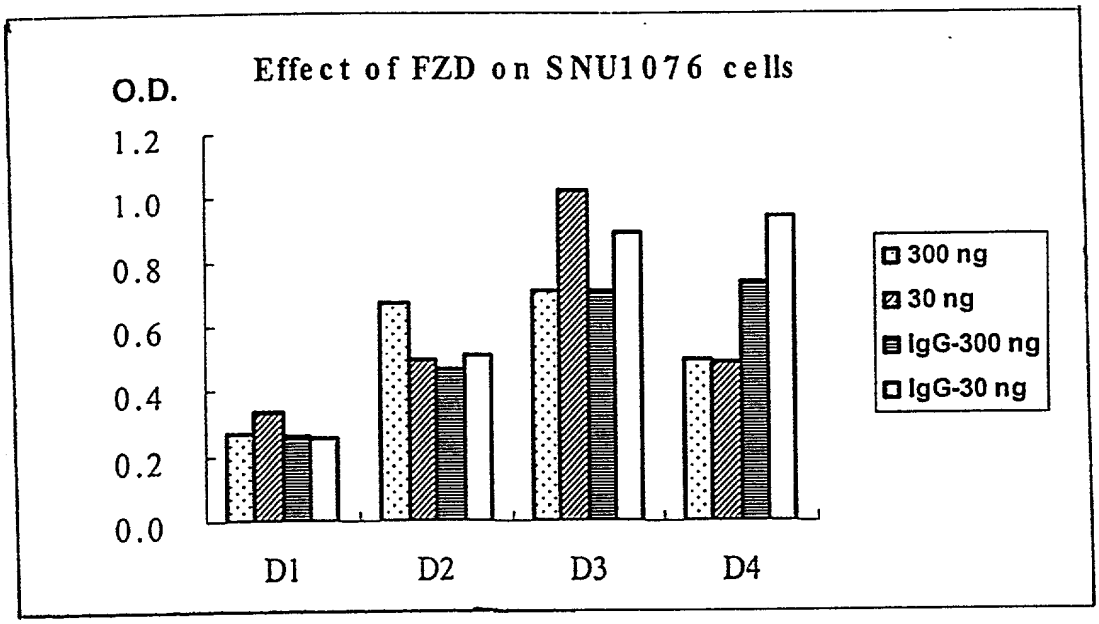

Effect of FZD on SNU1076 cells
O.D.
1.2
1.0
0.8
0.6
0.4
0.2
0.0
D1
D2
D3
D4
300 ng
30 ng
IgG-300 ng
IgG-30 ng

Figure 5

Effect of antibodies SNU 1076 Cells

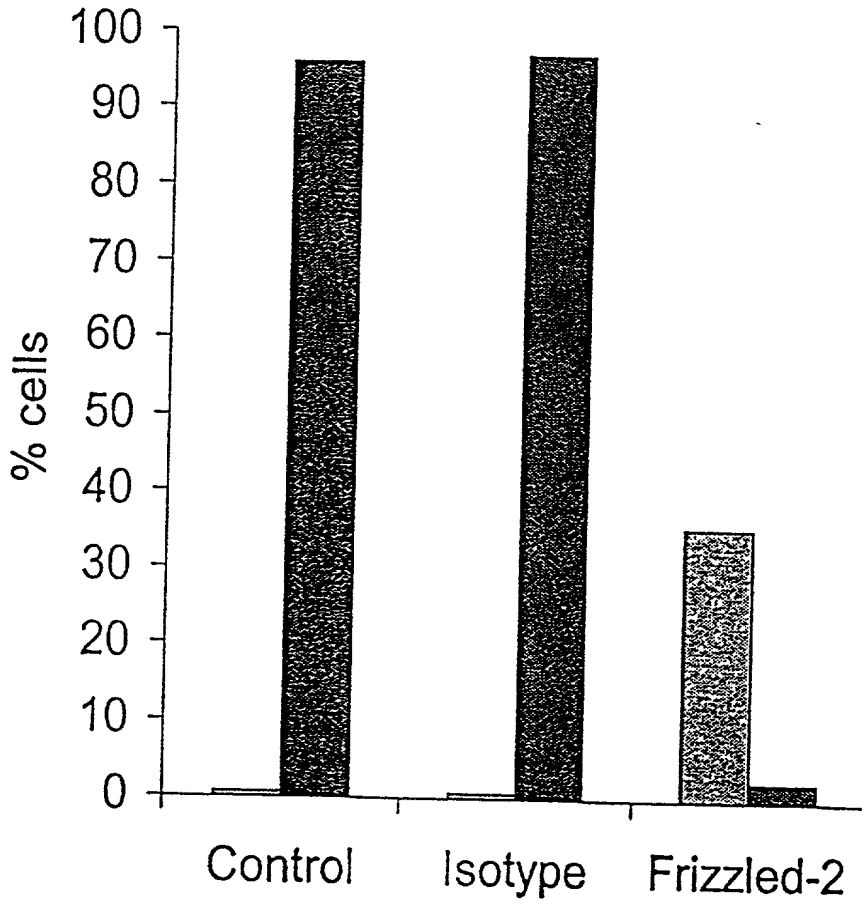


Figure 6

Effect of antibodies on SNU 1076 cells

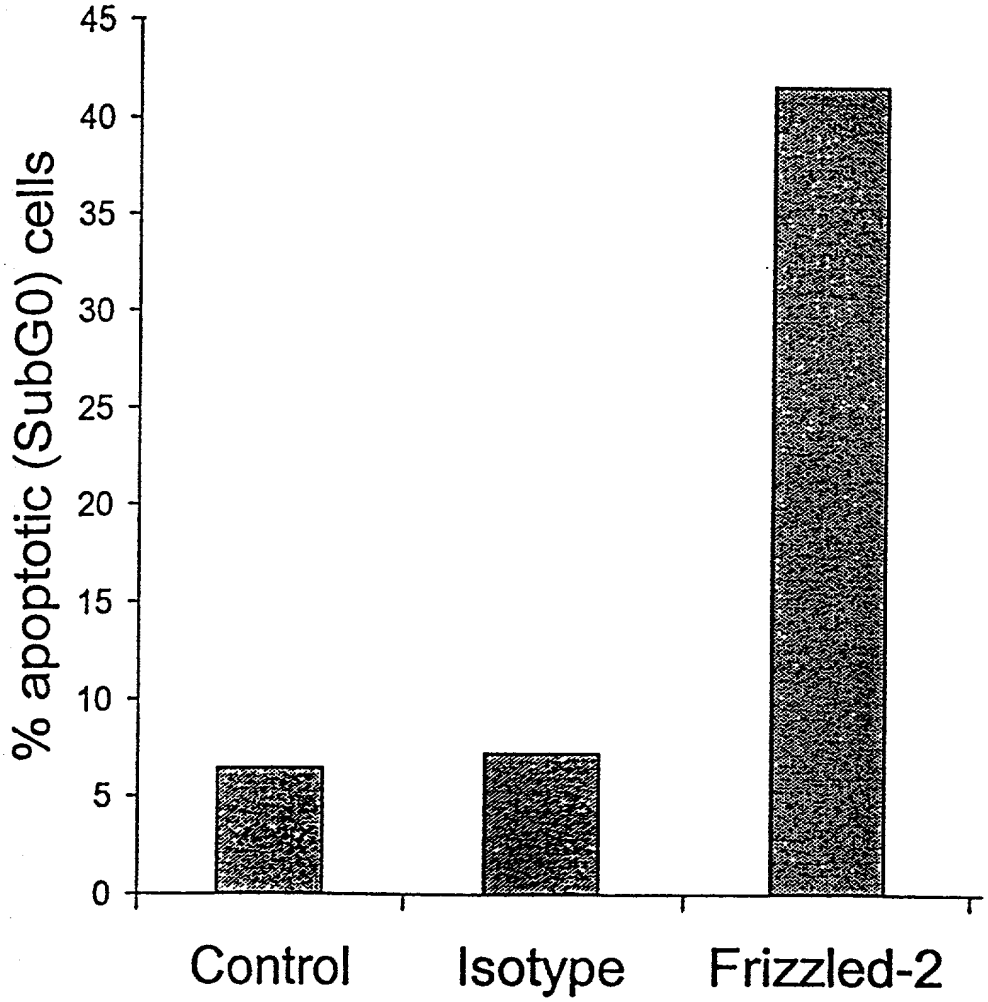
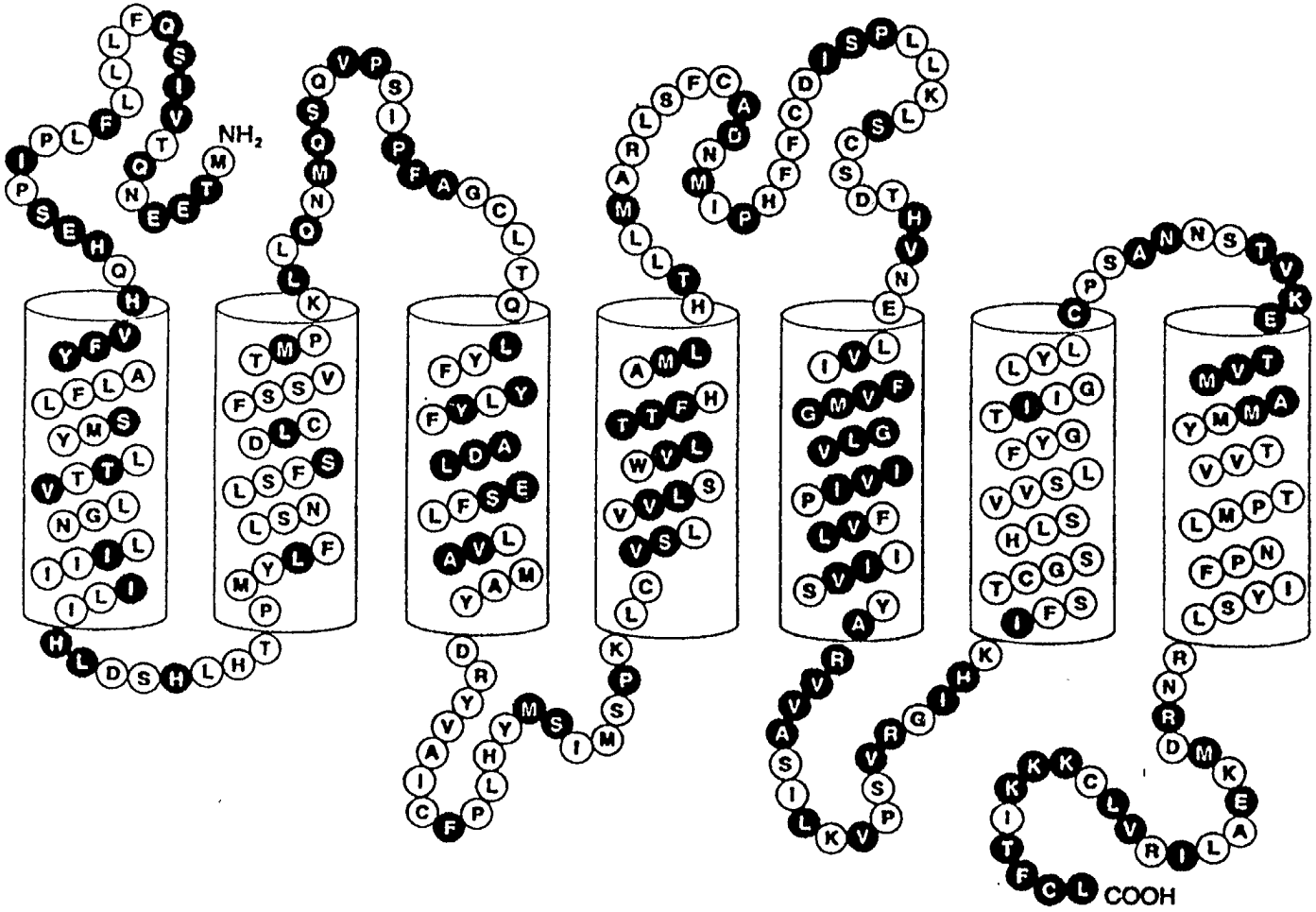


Figure 7



Graphical representation of an olfactory protein showing aminoterminal and three extracellular domain loops (from PCT WO 92/17585)

Figure 8a


|→ amino terminal domain
HFZ1 MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRRLARQLLLLLW
MFZ1 MAEEAAPSESRAAGR-LSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLW
HFZ2 -----MRPRSALPRLLLPLL
HFZ3 -----MAMTWIVFSLWPLTV
MFZ3 -----MAVSWIVFDLWLLTV
HFZ4 -----MAWRGAGPSVPGAPGGVGLSLGLLLQ
MFZ4 -----MAWPGTGPSSRGAPGGVGLRLGLLLQ
HFZ5 -----MARPDPSAPPSLL--LLL
HFZ6 -----MEMFTFLLTCI
MFZ6 -----MERSPFLLACI
HFZ7 -----MRDPGAAAPLSSLGLCALVLA
MFZ7 -----MRGPGTAASHSPLGLCALVLA
HFZ8 -----MEWGYLLEVTSLLAALAL
MFZ8 -----MEWGYLLEVTSLLAALAV
HFZ9 -----MAVAPL-RGALLLWQLLA
MFZ9 -----MAVPPLLRGALLLWQLLA
HFZ10 -----MQRPGPRLWLVLQ
HFZ1 LLEAPLLLGVRAQAAGQGPGQGPGPGQQPPPPPQQQQSGQQYNGERGISVPDHGYCQPIS
MFZ1 LLEAPLLLGVRAQAAGQVSG----PGQQAPPPPQPQQSGQQYNGERGISIPDHGYCQPIS
HFZ2 LLPA----------A----------GPAQFHGEKGISIPDHGFCQPIS
HFZ3 FMGHI----------GGHSLFS--------CEPIT
MFZ3 FLGQI----------GGHSLFS--------CEPIT
HFZ4 LLLLLG----------PARGFGDEEE------RRCDPIR
MFZ4 FLLLLR----------PTLGFGDEEE------RRCDPIR
HFZ5 LAQLVG----------RAAAASKAPV--------CQEIT
HFZ6 FLPLL----------RGHSLFT--------CEPIT
MFZ6 LLPLV----------RGHSLFT--------CEPIT
HFZ7 LLGAL----------SAGAGAQPYHGEKGISVPDHGFCQPIS
MFZ7 LLGAL----------PTDTRAQPYHGEKGISVPDHGFCQPIS
HFZ8 LQRSSG----------AAAASAKELA--------CQEIT
MFZ8 LQRSSG----------AAAASAKELA--------CQEIT
HFZ9 AGGAAL----------EIGRFDPERGR---GAAPCQAVE
MFZ9 TGGAAL----------EIGRFDPERGR---GPAPCQAME
HFZ10 VMGSCA----------AISSMDMERP----GDGKCQPIE
HFZ1 IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
MFZ1 IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCT-V
HFZ2 IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ3 LRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
MFZ3 LRMCQDLPYNTTFMPNLLNHYDQQTAALAMEPFHPMVNLDCSRDFRPFLCALYAPICM-E
HFZ4 ISMCQNLGYNVTKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMCTEK
MFZ4 IAMCQNLGYNVTKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMCTEK
HFZ5 VPMCRGIGYNLTHMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLRFFLCTMYTPICLPD
HFZ6 VPRCMKMAYNMTFFPNLMGHYDQSIAAVEMEHFLPLANLECSPNIETFLCKAFVPTCI-E
MFZ6 VPRCMKMTYNMTFFPNLMGHYDQGIAAVEMGHFLHLANLECSPNIEMFLCQAFIPTCT-E
HFZ7 IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
MFZ7 IPLCTDIAYNQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCT-V
HFZ8 VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPICLED
MFZ8 VPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPICLED

Figure 8b

```
HFZ9            IPMCRGIGYNLTRMPNLLGHTSQGEAAAELAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQ
MFZ9            IPMCRGIGYNLTRMPNLLGHTSQGEAAAQLAEFSPLVQYGCHSHLRFFLCSLYAPMCTDQ
HFZ10           IPMCKDIGYNMTRMPNLMGHENQREAAIQLHEFAPLVEYGCHGHLRFFLCSLYAPMCTEQ
                :  *  : ** * :** ..*  *  *  . :  *  : :  *  .:. ***  : * *

HFZ1            LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
MFZ1            LEQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHG--AGELCVGQNTSDKGT
HFZ2            LEQAIPPCRSICERARQGCEALMNKFGFQWPERLRCEHFPRHG--AEQICVGQNHSEDGA
HFZ3            YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLAG---
MFZ3            YGRVTLPCRRLCQRAYSECSKLMEMFGVPWPEDMECSRFPDCD-EPYPRLVDLNLVG---
HFZ4            INIPIGPCGGMCLSVKRRCEPVLKEFGFAWPESLNCSKFPPQN-DHNHMCMEGPGD----
MFZ4            INIPIGPCGGMCLSVKRRCEPVLREFGFAWPDTLNCSKFPPQN-DHNHMCMEGPGD----
HFZ5            YHKPLPPCRSVCERAKAGCSPLMRQYGFAWPERMSCDRLPVLGRDAEVLCMDYNRSEATT
HFZ6            QIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECDRLQYCD-ETVPVTFDPHTEF---
MFZ6            QIHVVLPCRKLCEKIVSDCKKLMDTFGIRWPEELECNRLPHCD-DTVPVTSHPHTEL---
HFZ7            LDQAIPPCRSLCERARQGCEALMNKFGFQWPERLRCENFPVHG--AGEICVGQNTSDGSG
MFZ7            LDQAIPPCRSLCERARQGCEALMNKFGFQWPERLRCENFPVHG--AGEICVGQNTSDGSG
HFZ8            YKKPLPPCRSVCERAKAGCAPLMRQYGFAWPDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
MFZ8            YKKPLPPCRSVCERAKAGCAPLMRQYGFAWPDRMRCDRLPEQG-NPDTLCMDYNRTDLTT
HFZ9            VSTPIPACRPMCEQARLRCAPIMEQFNFGWPDSLDCARLPTRN-DPHALCMEAPENA-TA
MFZ9            VSTPIPACRPMCEQARLRCAPIMEQFNFGWPDSLDCARLPTRN-DPHALCMEAPENA-TA
HFZ10           VSTPIPACRVMCEQARLKCSPIMEQFNFKWPDSLDCRKLPNKN-DPNYLCMEAPNN----
                      .*  :*      *  ::  :.. **: : * .:    .

HFZ1            PT---PSLLPEFWTSNPQHGGGGHRG-----------------------------------
MFZ1            PT---PSLLPEFWTSNGQHGGGGYRG-----------------------------------
HFZ2            -----PALLTTAPPPGLQPGAGGTPG-----------------------------------
HFZ3            ---EPTEGAPV---------------------------------------------------A
MFZ3            ---DPTEGAPV---------------------------------------------------A
HFZ4            ------EE------------------------------------------------------V
MFZ4            ------EE------------------------------------------------------V
HFZ5            APPRPFPAKPTLPG-------------PPGA-------------------PASGG-------
HFZ6            ---LGPQKKTE---------------------------------------------------Q
MFZ6            ---SGPQKKSD---------------------------------------------------Q
HFZ7            GPGGGPTAYPTAPYLPDLPFTALPPG-----------------------------------
MFZ7            GAGGSPTAYPTAPYLPDPPFTAMSP------------------------------------
HFZ8            AAPSPPRRLPPPPP-GEQPPSGSGHGRPPGARPPHRGGGRGGGGGDAAAPPARGGGGGGK
MFZ8            AAPSPPRRLPPPPPPGEQPPSGSGHSRPPGARPPHRGGSSRGSGDAAAAPPSRGG----K
HFZ9            GPAEPHKGLGMLPV------------------------------------------------A
MFZ9            GPTEPHKGLGMLPV------------------------------------------------A
HFZ10           GSDEPTRGSGLFPP------------------------------------------------L

HFZ1            GFPGGAG----ASERGKFSCPRALKVPSYLNYHFLGEKDCGAPCEPTKVYGLMYFGPEEL
MFZ1            GYPGGAG----TVERGKFSCPRALRVPSYLNYHFLGEKDCGAPCEPTKVYGLMYFGPEEL
HFZ2            GPGGGGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEET
HFZ3            VQRDYG-----------FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
MFZ3            VQRDYG-----------FWCPRELKIDPDLGYSFLHVRDCSPPCP----NMYFR--REEL
HFZ4            PLPHKTPI----------QPGEECHSVGTNSDQYIWVKRSLNCVLKCGYDAGLY-SRSAK
MFZ4            PLPHKTPI----------QPGEECHSVGSNSDQYIWVKRSLNCVLKCGYDAGLY-SRSAK
HFZ5            ECPAGGPFV--------CKCREPFVPILKESHPLYNKVRTGQVPNCAVPCYQPSFSADER
HFZ6            VQRDIG-----------FWCPRHLKTSGGQGYKFLGIDQCAPPCP----NMYFK--SDEL
MFZ6            VPRDIG-----------FWCPKHLRTSGDQGYRFLGIEQCAPPCP----NMYFK--SDEL
HFZ7            ASDGRGRPAF------PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
MFZ7            -SDGRGRLSF------PFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYFKEEER
HFZ8            ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFFSQDER
MFZ8            ARPPGGGAAP---CEPGCQCRAPMVSVSSERHPLYNRVKTGQIANCALPCHNPFFSQDER
HFZ9            PRPARPPG--------DLGPGAGGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSRRDK
MFZ9            PRPARPPG--------DSAPGPGSGGTCDNPEKFQYVEKSRSCAPRCGPGVEVFWSRRDK
HFZ10           FRPQRPHSAQ----EHPLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDK
```

Figure 8c

```
                    <-|
HFZ1     RFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYTAVAVAYIAGFLLE
MFZ1     RFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSGCYTAVAVAYIAGFLLE
HFZ2     RFARLWILTWSVLCCASTFFTVTTYLVDMQRFRYPERPIIFLSGCYTMVSVAYIAGFVLQ
HFZ3     SFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE
MFZ3     SFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCYMMVSLIFFIGFLLE
HFZ4     EFTDIWMAVWASLCFISTAFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
MFZ4     EFTDIWMAVWASLCFISTTFTVLTFLIDSSRFSYPERPIIFLSMCYNIYSIAYIVRLTVG
HFZ5     TFATFWIGLWSVLCFISTSTTVATFLIDMDTFRYPERPIIFLSACYLCVSLGFLVRLVVG
HFZ6     EFAKSFIGTVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFIGFLLG
MFZ6     DFAKSFIGIVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFVGFLLG
HFZ7     RFARLWVGVWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYFMVAVAHVAGFLLE
MFZ7     RFARLWVGVWSVLSCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYFMVAVAHVAGFLLE
HFZ8     AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG
MFZ8     AFTVFWIGLWSVLCFVSTFATVSTFLIDMERFKYPERPIIFLSACYLFVSVGYLVRLVAG
HFZ9     DFALVWMAVWSALCFFSTAFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
MFZ9     DFALVWMAVWSALCFFSTAFTVFTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAG
HFZ10    RFAVVWLAIWAVLCFFSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSVGYLIRLFAG
          *:  ::   : :.  ::  *. *:*::   * *******  : **   :: ..
         |->   extracellular domain loop 1
HFZ1     DRVVCNDK-----------------------------------FAEDGARTVAQGTKK
MFZ1     DRVVCNDK-----------------------------------FAEDGARTVAQGTNK
HFZ2     ERVVCNER-----------------------------------FSEDGYRTVVQGTKK
HFZ3     DRVACNAS--------------------------------I---PAQYKASTVTQGSHN
MFZ3     DRVACNAS--------------------------------S---PAQYKASTVTQGSHN
HFZ4     RERISCDF-----------------------------------EEAAEPVLIQEGLKN
MFZ4     RERISCDF-----------------------------------EEAAEPVLIQEGLKN
HFZ5     HASVACS-----------------------RE---------------HNHIHYETTGP
HFZ6     DSTACNKA--------------------------------D---EKLELGDTVVLGSQN
MFZ6     NSTACNKA--------------------------------D---EKLELGDTVVLGSKN
HFZ7     DRAVCVER-----------------------------------FSDDGYRTVAQGTKK
MFZ7     DRAVCVER-----------------------------------FSDDGYRTVAQGTKK
HFZ8     HEKVACSGGAPGAGGAGGAGGAAA-GAGAAGAGAGGPGGRGEYEELGAVEQHVRYETTGP
MFZ8     HEKVACSGGAPGAGGRGGAGGAAAAGAGAAGRGASSPGARGEYEELGAVEQHVRYETTGP
HFZ9     AQSVACD------------------------------------QEAGALYVIQEGLEN
MFZ9     AQSVACD------------------------------------QEAGALYVIQEGLEN
HFZ10    AESIACD------------------------------------RDSGQLYVIQEGLES

              <-|
HFZ1     EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
MFZ1     EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKT
HFZ2     EGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ3     KACTMLFMILYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
MFZ3     KACTMLFMVLYFFTMAGSVWWVILTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLT
HFZ4     TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
MFZ4     TGCAIIFLLMYFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKT
HFZ5     ALCTIVFLLVYFFGMASSIWWVILSLTWFLAAAMKWGNEAIAGYGQYFHLAAWLIPSVKS
HFZ6     KACTVLFMLLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGTPGFLT
MFZ6     KACSVVFMFLYFFTMAGTVWWVILTITWFLAAGRKWSCEAIEQKAVWFHAVAWGAPGFLT
HFZ7     EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
MFZ7     EGCTILFMVLYFFGMASSIWWVILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAVKT
HFZ8     ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIAGYSQYFHLAAWLVPSVKS
MFZ8     ALCTVVFLLVYFFGMASSIWWVILSLTWFLAAGMKWGNEAIAGYSQYFHLAAWLVPSVKS
HFZ9     TGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
MFZ9     TGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMAAWGLPALKT
HFZ10    TGCTLVFLVLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEANSSYFHLAAWAIPAVKT
           *:::*:.:*:* **.::***:*::******  **. ***    .  **  **  *.  :
               |-> extracellular domain loop 2  <-|
HFZ1     ITILALGQVDGDVLSGVCFVGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ1     ITILALGQVDGDVLSGVCFLGLNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ2     ITILAMGQIDGDLLSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ3     IILLAMNKIEGDNISGVCFVGLYDVDALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE
MFZ3     IILLAMNKIEGDNISGVCFVGLYDVDALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIE
```

Figure 8d

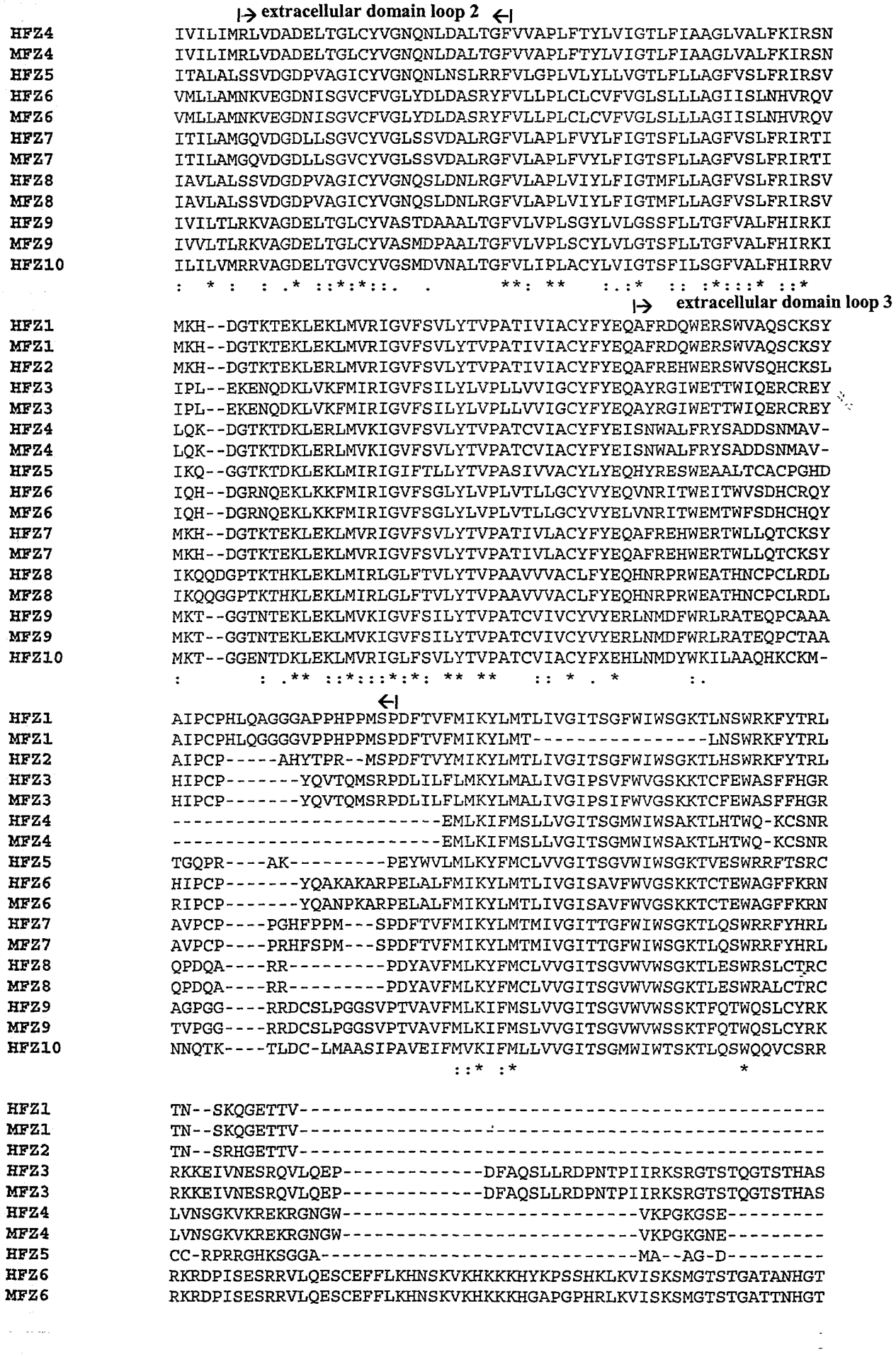

|→ extracellular domain loop 2 ←|
HFZ4 IVILIMRLVDADELTGLCYVGNQNLDALTGFVVAPLFTYLVIGTLFIAAGLVALFKIRSN
MFZ4 IVILIMRLVDADELTGLCYVGNQNLDALTGFVVAPLFTYLVIGTLFIAAGLVALFKIRSN
HFZ5 ITALALSSVDGDPVAGICYVGNQNLNSLRRFVLGPLVLYLLVGTLFLLAGFVSLFRIRSV
HFZ6 VMLLAMNKVEGDNISGVCFVGLYDLDASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
MFZ6 VMLLAMNKVEGDNISGVCFVGLYDLDASRYFVLLPLCLCVFVGLSLLLAGIISLNHVRQV
HFZ7 ITILAMGQVDGDLLSGVCYVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
MFZ7 ITILAMGQVDGDLLSGVCYVGLSSVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTI
HFZ8 IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
MFZ8 IAVLALSSVDGDPVAGICYVGNQSLDNLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSV
HFZ9 IVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLLTGFVALFHIRKI
MFZ9 IVVLTLRKVAGDELTGLCYVASMDPAALTGFVLVPLSCYLVLGTSFLLTGFVALFHIRKI
HFZ10 ILILVMRRVAGDELTGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVALFHIRRV
|→ extracellular domain loop 3
HFZ1 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
MFZ1 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSY
HFZ2 MKH--DGTKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHWERSWVSQHCKSL
HFZ3 IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY
MFZ3 IPL--EKENQDKLVKFMIRIGVFSILYLVPLLVVIGCYFYEQAYRGIWETTWIQERCREY
HFZ4 LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-
MFZ4 LQK--DGTKTDKLERLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAV-
HFZ5 IKQ--GGTKTDKLEKLMIRIGIFTLLYTVPASIVVACYLYEQHYRESWEAALTCACPGHD
HFZ6 IQH--DGRNQEKLKKFMIRIGVFSGLYLVPLVTLLGCYVYEQVNRITWEITWVSDHCRQY
MFZ6 IQH--DGRNQEKLKKFMIRIGVFSGLYLVPLVTLLGCYVYELVNRITWEMTWFSDHCHQY
HFZ7 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
MFZ7 MKH--DGTKTEKLEKLMVRIGVFSVLYTVPATIVLACYFYEQAFREHWERTWLLQTCKSY
HFZ8 IKQQDGPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
MFZ8 IKQQGGPTKTHKLEKLMIRLGLFTVLYTVPAAVVVACLFYEQHNRPRWEATHNCPCLRDL
HFZ9 MKT--GGTNTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCAAA
MFZ9 MKT--GGTNTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRATEQPCTAA
HFZ10 MKT--GGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFXEHLNMDYWKILAAQHKCKM-
←|
HFZ1 AIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRL
MFZ1 AIPCPHLQGGGGVPPHPPMSPDFTVFMIKYLMT----------LNSWRKFYTRL
HFZ2 AIPCP-----AHYTPR--MSPDFTVYMIKYLMTLIVGITSGFWIWSGKTLHSWRKFYTRL
HFZ3 HIPCP-------YQVTQMSRPDLILFLMKYLMALIVGIPSVFWVGSKKTCFEWASFFHGR
MFZ3 HIPCP-------YQVTQMSRPDLILFLMKYLMALIVGIPSIFWVGSKKTCFEWASFFHGR
HFZ4 ----------EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
MFZ4 ----------EMLKIFMSLLVGITSGMWIWSAKTLHTWQ-KCSNR
HFZ5 TGQPR----AK---------PEYWVLMLKYFMCLVVGITSGVWIWSGKTVESWRRFTSRC
HFZ6 HIPCP-------YQAKAKARPELALFMIKYLMTLIVGISAVFWVGSKKTCTEWAGFFKRN
MFZ6 RIPCP-------YQANPKARPELALFMIKYLMTLIVGISAVFWVGSKKTCTEWAGFFKRN
HFZ7 AVPCP----PGHFPPM---SPDFTVFMIKYLMTMIVGITTGFWIWSGKTLQSWRRFYHRL
MFZ7 AVPCP----PRHFSPM---SPDFTVFMIKYLMTMIVGITTGFWIWSGKTLQSWRRFYHRL
HFZ8 QPDQA----RR---------PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRSLCTRC
MFZ8 QPDQA----RR---------PDYAVFMLKYFMCLVVGITSGVWVWSGKTLESWRALCTRC
HFZ9 AGPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLCYRK
MFZ9 TVPGG----RRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLCYRK
HFZ10 NNQTK----TLDC-LMAASIPAVEIFMVKIFMLLVVGITSGMWIWTSKTLQSWQQVCSRR
HFZ1 TN--SKQGETTV----------
MFZ1 TN--SKQGETTV----------
HFZ2 TN--SRHGETTV----------
HFZ3 RKKEIVNESRQVLQEP----------DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
MFZ3 RKKEIVNESRQVLQEP----------DFAQSLLRDPNTPIIRKSRGTSTQGTSTHAS
HFZ4 LVNSGKVKREKRGNGW----------VKPGKGSE---------
MFZ4 LVNSGKVKREKRGNGW----------VKPGKGNE---------
HFZ5 CC-RPRRGHKSGGA----------MA--AG-D---------
HFZ6 RKRDPISESRRVLQESCEFFLKHNSKVKHKKKHYKPSSHKLKVISKSMGTSTGATANHGT
MFZ6 RKRDPISESRRVLQESCEFFLKHNSKVKHKKKHGAPGPHRLKVISKSMGTSTGATTNHGT

Figure 8e

```
HFZ7        SH--SSKGETAV-------------------------------------------------
MFZ7        SH--SSKGETAV-------------------------------------------------
HFZ8        CW-ASKGAAVGGGAGA---------------------------TAAGGGGGPGGGGGGGP
MFZ8        CW-ASKGAAVGAGAGG---------------------------SGPGGSGP-------GP
HFZ9        IA--AGRARAKACRAP---------------------------GSYGRGTHC--------
MFZ9        MA--AGRARAKACRTP---------------------------GGYGRGTHC--------
HFZ10       LKKKSRRKPASVITSG---------------------------GIYKKAQH---------

HFZ1        ------------------------------------------------------------
MFZ1        ------------------------------------------------------------
HFZ2        ------------------------------------------------------------
HFZ3        STQLAMVDDQRSKAGSIHSKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
MFZ3        STQLAMVDDQRSKAGSVHSKVSSYHGSLHRSRDGRYTPCSYRG--MEERLPHGSMS-RLT
HFZ4        -------------------TVV--------------------------------------
MFZ4        -------------------TVV--------------------------------------
HFZ5        -------------YPEASAALTGRTGPPGPAATYHKQVSLSHV-----------------
HFZ6        SAVAITSHDYLGQETLTEIQTSPETSMREVKADGASTPRLREQDCGEPASPAASIS-RLS
MFZ6        SAMAIADHDYLGQETSTEVHTSPEASVKEGRADRANTPSAKDRDCGESAGPSSKLSGNRN
HFZ7        ------------------------------------------------------------
MFZ7        ------------------------------------------------------------
HFZ8        GGGGGPGGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----------------
MFZ8        GGGGGHGGGGGSLYSDVSTGLTWRSGTAS-SVSYPKQMPLSQV-----------------
HFZ9        -----------H---YKAPTVVLHMTKTDPSLENPTHL----------------------
MFZ9        -----------H---YKAPTVVLHMTKTDPSLENPTHL----------------------
HFZ10       ------------------PQKT-HHGKYEIPAQSPTCV----------------------

HFZ1        ------------------------------------------------------------
MFZ1        ------------------------------------------------------------
HFZ2        ------------------------------------------------------------
HFZ3        DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA------------
MFZ3        DHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA------------
HFZ4        ------------------------------------------------------------
MFZ4        ------------------------------------------------------------
HFZ5        ------------------------------------------------------------
HFZ6        GEQVDGKG--QAGSVSESARSEGRISPKSDITDTGLAQSNNLQVPSSSEPSSLKGSTSLL
MFZ6        GRESRAGGLKERSNGSEGAPSEGRVSPKSSVPETGLIDCSTSQAASSPEPTSLKGSTSLP
HFZ7        ------------------------------------------------------------
MFZ7        ------------------------------------------------------------
HFZ8        ------------------------------------------------------------
MFZ8        ------------------------------------------------------------
HFZ9        ------------------------------------------------------------
MFZ9        ------------------------------------------------------------
HFZ10       ------------------------------------------------------------

HFZ1        ------------------
MFZ1        ------------------
HFZ2        ------------------
HFZ3        ------------------
MFZ3        ------------------
HFZ4        ------------------
MFZ4        ------------------
HFZ5        ------------------
HFZ6        VHPVSGVRKEQGGGCHSDT
MFZ6        VHSASRARKEQGAGSHSDA
HFZ7        ------------------
MFZ7        ------------------
HFZ8        ------------------
MFZ8        ------------------
HFZ9        ------------------
```